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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/355,793	09/21/99	BLASER M	D5979

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EXAMINER	
PORTNER, V	
ART UNIT	**PAPER NUMBER**
1645	13

DATE MAILED: 09/27/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/335,793	Blaser
Examiner	**Art Unit**
Portner	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 29, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 5-13, and 15-18* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 5-13, and 15-18* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Claims 2-4 and 14 have been canceled.

Claims 1, 5-13, and 15-18 are pending.

Claims 1, 15, 16, 17 and 18 have been amended.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Allowable Subject Matter

2. The previously indicated allowable subject matter defined to be in claim 15, is herein withdrawn in view of the fact that Applicant has not obviated the rejection made under 35 U.S.C. 112, first paragraph (Deposit requirement), and new grounds of rejection set forth below.

Rejections Withdrawn

3. Claims 8 and 14 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, in view of the amendment of claim 1 to recite the phrase heterologous protein, and claim 14 having been canceled.

4. Claim 1 rejected under 35 U.S.C. 112, first paragraph (new matter), as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, in light of the claim having been amended to recite the phrase "A genetically engineered mutant".

5. Claim 16 rejected under 35 U.S.C. 102(b) as being anticipated by Dworkin et al (June 1995) , in light of claim 16 being amended to depend from claim 15, which is directed to a mutant E.coli strain and not a mutant C.fetus strain.

6. Claims 1, 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Blaser November 1993, in light of the amendment of the claims to require the cassette to encode a heterologous protein.

7. Claims 1, 5-8 rejected under 35 U.S.C. 103(a) as being unpatentable over Blaser (1994 cited above.) in view of Szostak et al (1996) in light of the amendment of the claims to require surface expression of the heterologous antigen.

Rejections Maintained

8. Claims 10-13, 15-17 rejected under 35 U.S.C. § 112, first paragraph (Deposit), for the reasons set forth in the objection to the specification for reasons of record in paper number 6.

9. Claim 18 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons of record in paper number 10, paragraph 30.

10. Claims 1, 6-8 are rejected under 35 U.S.C. 102(a) as being anticipated by Dworkin et al (March 1996) for reasons of record in paper number 6.

11. Claims 1, 6-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Blaser (November 1994) for reasons of record in paper number 6.

12. Claims 1, 5-9 rejected under 35 U.S.C. 103(a) as being unpatentable over of Blaser (1994 cited above.) in view of Lubitz et al (US pat. 5,470,573) for reasons of record in paper number 6.

Response to Arguments

13. Applicant, in response to the request for clarification of incorporation by reference of essential material, states the material incorporated by reference is directed to non-essential subject matter.

14. It is the position of the examiner that incorporation of non-essential subject matter is not improper.

15. The rejection of Claims 10-17 under 35 U.S.C. § 112, first paragraph (Deposit), is argued to have enabled the person skilled in the art on how to make and use the claimed inventions in "Examples 4 and 9, wherein the reagents required are known to those having ordinary skill in this art as described by Example 4".

16. It is the position of the examiner that the RecA protein was known for Campylobacter jejuni and the DNA for this gene encoded product could readily be ascertained but the **gene sequence** for the **RecA protein** of **Campylobacter fetus was not** in the **public domain** at the time of filing of the priority document dated January 31, 1997. Tummuru et al in 1993 suggested the presence of a putative Chi (RecBCD recognition) site upstream of sapA, sapA1 and sapA2 and suggested a system of homologous recombination, but this does not put the gene in the public domain because the RecA protein and the nucleic acid sequence encoding it were only postulated to be present. A suggestion of a gene does not define its existence, nor does it isolate and purify the gene or teach how to make and use the gene. Mutants of the RecA gene of Campylobacter fetus would

therefore need to be deposited because the specific gene sequence was not described until after the filing date of the priority document.

In response to Applicant's assertion that a Deposit requirement for modified bacteria that express SapCDEF genes is not needed in view of the guidance provided in the instant specification has been fully considered but has not been found persuasive because the journal reference submitted was published after the time of filing the instant specification and contains additional information not contained within the instant specification.. The submitted reference does not provide for enablement of the claimed invention at the time of filing.

Upon consideration of Examples 4 and 9 of the instant specification, the examiner found several references incorporated by reference that provide for guidance for methods and the use of reagents to carry out specific methods steps, but the plasmids recited in Example 4 were not disclosed in the prior art, nor were the gene sequences disclosed. Example 9 refers to strain 23D as the source of the claimed genetic material expressed in modified bacteria. The strain, from which the open reading frames were isolated, was not defined as a publicly available strain of C.fetus and therefore does not meet the requirements under the Budapest Treaty. The only strain disclosed for attainment of the SapCDEF open reading frames of C. fetus is strain 23D. No other strains were used in the attainment of these genes. In view of the prior art, as well as the instant specification, teaching that natural recombination within Campylobacter fetus is a well established fact, the use of the disclosed restriction enzymes in an attempt to pull out the genes contained in the claimed modified strain of bacteria would not be predictable nor repeatable.

While strain 23D was described, the strain did not meet the Deposit requirement under the Budapest Treaty. Deposit of the strain that comprises the SapCDEF genes so they could be obtained by the method of the instant specification would meet the enablement requirement for the claimed invention. Deposit of the plasmids that encode the genes for SapC, SapD, SapE and SapF would also define a means for providing a repeatable method for obtaining strains of bacteria that would express these genes, an alternative means for meeting the enablement of the claimed modified bacteria that express SapCDEF genes. The instant specification does not teach that any strain of C.fetus may be used for the attainment for the recited genes using the disclosed restriction endonuclease patterns. Only C.fetus, strain 23D has been described in such a way that one of skill in the art could use this strain to obtain the claimed genes to produce a modified (transformed host cell) bacteria. The genetic material contained in the claimed genes is defined by the strain from which it was obtained in view of the high degree of genetic recombination that this locus undergoes. The Deposit requirement is maintained.

17. The rejection of claim 18 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is traversed n light of the claim having been amended to recite the phrase "seven to nine sapA homologs".

18. It is the position of the examiner that the rejection of claim 18 made of record in paper number 10, paragraph 30, is partially obviated through the submitted claim amendment, but the

claim was unclear because claim 1 does not provide antecedent basis for the phrase "the sapA **homologs**", but recites the word "homolog" in the singular.

19. Applicant argues the rejection of claims 1-2, 6-8 under 35 U.S.C. 102(a) as being anticipated by Dworkin et al (March 1996) by asserting Dworkin did not teach or suggest making and using mutant strains that express foreign heterologous protein, wherein a "DNA cassette encoding a foreign heterologous protein alters a sapA homolog and the expression of the DNA cassette results in a S-layer protein that represents a chimera between the native S-layer protein and the heterologous protein.

20. Applicant's arguments filed with respect to Dworkin et al have been fully considered but they are not persuasive because Dworkin et al teach mutant strains that have not been structurally mutated (see figure 3a,3b, 7 and Table 1) . Inherently the mutant strain of Dworkin anticipates the now claimed invention, in light of reading claim 1 to recite conditional limitations, "wherein the insertion of said DNA cassette results in alteration of a sapA homolog", that need not be contained in the mutant strains, but must take place when the insertion is carried out.

21. Claims 1, 6-8 rejected under 35 U.S.C. 102(b) as being anticipated by Blaser (November 1994 1993) is asserted that the expression of the DNA cassette encoding a foreign heterologous protein results in the surface expression of a chimera.

22. Applicant's arguments filed with respect to Blaser (1994) have been fully considered but they are not persuasive because the composition of Blaser comprised an antigenic, therapeutic agent, that encoded for kanamycin resistance and the claim limitations argued are conditional limitations. The strain must contain the DNA cassette, but the additional "wherein" clause is only a required functional limitation for when the DNA cassette is inserted to alter a sapA homolog. The claimed invention is a C.fetus strain that comprises a DNA expression cassette encoding any heterologous protein antigen or therapeutic agent. Applicant's arguments are not commensurate in scope with the structural and functional components required for the claimed mutant C.fetus strain. The rejection made of record is maintained.

23. The rejection of claims 1, 5-9 under 35 U.S.C. 103(a) as being unpatentable over Blaser (1994 cited above.) in view Lubitz et al (US pat. 5,470,573) is argued by asserting Blaser to teach away from the claimed invention, wherein the chimera is expressed on the surface of the bacteria.

24. It is the position of the examiner that Blaser teaches that the genetic mutant strains reverted to a phenotype that produced the S-layer and still contained the DNA cassette for the heterologous antigen, through southern blotting the showed rearrangement of the DNA to express SapA and retention of the kanamycin heterologous antigen

25. Applicant argued that the C.fetus strains were not evaluated with respect to the immune system of a mammalian host.

26. In response, it is the position of the examiner that Blaser administered the genetically engineered strain to mice, a mammalian host, and evaluated the level of bacteremia induced, which is a type of evaluation of the animals immune system against infection. The foreign antigens presented by C.fetus would stimulate an immune response in the mammalian host.

27. Lubitz et al is argued to teach away because the reference does not involve modification of sap homologs in C.fetus and the use of bacterial ghosts carry immunogens in the bacterial membrane and not in the S-layer coat.

28. It is the position of the examiner the Lubitz et al do not teach away from the claimed invention, wherein the reference teaches the incorporation of an immunogen in to the S-layer coat of the bacterial strain (see col. 2, lines 24-26) and Figure 2d, wherein the figure shows the expression of the chimeric heterologous immunogen in the cell wall complex, which is the outer membrane, contrary to Applicant's assertion.

With respect to the mutant strains being ghosts, it is the position of the examiner that the claimed invention is not limited to a living mutant cell and encompasses within the scope of the claims mutant strains that will produce bacterial ghosts, and serve as a non-living immunogen. The mutant strains are not claimed to be a living vaccine strain.

The composition of **Blaser** comprised an antigenic, therapeutic agent, specifically kanamycin, a heterologous antigen. The compositions were administered to a host animal for challenge experiments, thus stimulating an immune response. The reference used the strain to

evaluate the in vivo characteristics of sapA mutant C.fetus cells through administering the strain to a mammal. Virulence was evaluated through determining the number of cells required to cause bacteremia relative to wild type strains. The reference clearly is evaluating antigenic characteristics of the strains, virulence characteristics and the immune response stimulated in the host through challenge experiments using the mutant strains. The claimed method is not a method of vaccinating, but a method of stimulating an immune response.

Clearly Lubitz does not teach away from the construction of a mutant Campylobacter strain that comprises an S-layer and comprises an expressed heterologous antigen that is encoded by a DNA cassette. Blaser clearly teaches the use of C.fetus as a strain that is useful for the evaluation of the immune system of a mammalian host and in evaluating the immune response to antigens expressed (immunoblot). Therefore, Lubitz and Blaser are analogous art.

Both Blaser and Lubitz teach and suggest the evaluation of expressed heterologous antigens, as well as the construction of mutant strains of bacteria that comprise DNA cassettes that comprise a heterologous antigen, wherein the mutant strain is a Campylobacter strain. Both C.fetus and C.jejuni are both taught to be useful Campylobacter strains for the expression of a DNA cassette that encodes a heterologous antigen.

In response to applicant's arguments against the references individually, one **cannot show** nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Absent a showing of unexpected results, the applied prior art obviates the now claimed invention for reasons of record.

New claim limitations/New Grounds of Rejection

29. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

30. Claims 15-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a scope of written description rejection.*

The specification broadly describes as part of the invention isolated polynucleotides comprising four open reading frames for the sapCDEF coding sequences of C.fetus, strain 23D (see page 19, Example 13). The specification does not refer to the novel open reading frames by reference to a polynucleotide SEQ ID NO. The specification broadly describes polynucleotides encoding SapC, SapD, SapE, SapF, may contain additional coding and non coding regions, and that such language is intended to encompass the "gene" and those coding or non-coding sequences. Applicant also broadly describe the invention as embracing homologs and chimeric proteins that contain nucleic acid sequences that are heterologous to C.fetus (claim 16) which can

be changed. The genetically engineered host cells are taught for producing the heterologous antigen. What the nucleic acid sequences are that encode the recited genes has not been described based upon a specific nucleic acid sequence. None of these sequences meets the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

The specification only discloses a polynucleotide sequence that was cloned into specific vectors and was obtained from a specific strain of C.fetus that has not been deposited under the Budapest treaty. Only a deposited strain or plasmid the contains the four open reading frames, would meet the written description provision of 35 U.S.C. 112, first paragraph.

Applicants have not described nor disclosed the "operon" which encodes the all of the sapA homologs and the genes that encode them. A functional bacterial gene encompasses much more than a protein coding region (see Davis et al., Microbiology, page 267). A bacterial gene is conventionally associated with positive and negative controlling elements such as promoters and repressors in a concordantly regulated transcription unit called an operon, without which, no protein is expressed. The specification fails to describe the functional gene *per se* (i.e., operon) and which applicants have intended to be encompassed by the comprising and encoding language

of the instant claims as set forth *supra*. In a bacterial genome, the recitation of "comprising", includes regulatory sequences which are essential to the operation and function of the structural gene in the operon. These regulatory and other gene sequences of the operon that are not described, are essential to the function of the structural gene within the operon and are therefore essential elements. Such sequences fail to have an adequate written description in the instant specification. The specification does not provide written description support for any flanking nucleic acid sequences which are 5' or 3' of sapCDEF. The skilled artisan cannot envision all the contemplated nucleotide sequences by the detailed chemical structure of the claimed polynucleotides and therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Therefore, only an isolated polynucleotide consisting of an isolated polynucleotide encoding sapCDEF contained in a deposited plasmid or strain from which sapCDEF can be obtained could meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35

U.S.C. 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

31. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

32. Claims 1, 5-13, 15, 16 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the phrase "wherein said strain is mutated to contain a DNA cassette encoding a" twice, this is confusing.

Claim 1 recites that the Campylobacter fetus contains a DNA cassette that encodes a heterologous protein. While this statement is clear, in light of the newly submitted "wherein clause", it is not clear what is contained in the mutant strain. The second "wherein" statement is "wherein the insertion of said DNA cassette results in alteration of a sapA homolog". This phrase is in the future tense, thus the claimed mutant does not comprise the DNA cassette that is recited in the first "wherein" statement. The combination of claim limitations and clarification phrases are not in agreement one with another. This rejection could be obviated by amending the claim to

recite "comprising" language setting forth the specific components that the mutant strain comprises. (ie. sapA homolog into which a heterologous protein coding sequence has been inserted, operatively linked to a promoter sequence for the expression and surface incorporation of the S-layer protein/heterologous protein complex; or an equivalent phrase that clearly sets forth Applicant's invention that is not New Matter).

Claim 5 clarifies that the DNA cassette encodes immunogens of a pathogen. The word "immunogen" lacks antecedent basis in claim 1 that has been amended to recite the phrase "heterologous protein". Amendment of claim 5 to recite --wherein the encoded heterologous protein is an immunogen--.

Claim 6 defines where the protein is inserted. This is confusing because the DNA coding sequence is what is inserted, not a protein. While it is clear that the DNA cassette contains a 5' binding region and a 3' secretion region, what these ends correspond to is not distinctly claimed. What sequence is the coding sequence for the heterologous protein inserted into? How does the cassette of claim 1, from which claim 6 depends accomplish expression of the binding region and the secretion signal into which the heterologous coding sequence has been inserted? No specific sequences have been recited in any of the claims, what the binding region and the secretion region are based upon the claimed DNA cassette is not clearly set forth in the claim.

Claim 7 defines the cassette to contain a 3' secretion signal and not binding region and does not say anything about where the heterologous protein is with respect to the secretion signal. Does the cassette of claim 7 broaden the scope of claim 1 to omit the heterologous protein coding

sequence, as the claimed C.fetus strain only contains a secretion signal ? To what is the 3' secretion signal associated? There must be a 5' sequence of some kind, what is the 5' sequence? How do any of the sequences get expressed without a promoter? Where is the DNA cassette? If it in the chromosome of the C.fetus strain, the addition of a promoter would not need to be recited because the native promoter would function to express the cassette, but if the cassette is a plasmid, then the heterologous protein coding sequence would need to be in association with a promoter to achieve expression. Clarification of where the DNA cassette is located relative to the recited 3' secretion signal sequence, what the 3' secretion signal sequence is associated and how the heterologous protein and the 3' secretion signal sequence are expressed is requested.

Claim 8 depends from claim 1 and defines the heterologous protein to be an antigen or therapeutic agent. While it is clear that heterologous proteins are antigens, how does the recited therapeutic agent differ from the antigen recited in the claim? Is the therapeutic agent an antigen? If it is not an antigen, what kind of protein is it? What is the therapeutic agent, in light of claim 1 having been amended to recite the phrase heterologous protein?

Claim 9 immunizes a host with an immunogen. The term immunogen lacks antecedent basis in claim 1 from which claim 9 depends. Is the C.fetus strain the immunogen? The strain of claim 1 is not claimed as comprising a DNA cassette that encodes a heterologous protein sequence that is an immunogen and is operatively linked to a promoter for expression of the heterologous protein. Claim 1 states "wherein the insertion of said DNA cassette results in", but this is a conditional phrase that functionally takes place, when the step is carried out. Is the

immunogen the heterologous protein or the C.fetus strain or both? Claim 1 does not define a mutant strain in which the cassette has been inserted and encodes a heterologous protein. In view of claim 1 not being clear, the immunogen and the pharmacologically effective dose of claim 9 is also not clearly defined.

Claim 10 is directed to a mutant strain of C.fetus. The strain does not comprise a functional RecA protein. The phrase "the DNA rearrangements permitting sapA antigenic variation occur at a very low frequency". This phrase appears to lack the word --to-- before the word "occur". Claim 10 also defines the strain to only produce one of the S-layer proteins encoded by one sapA homolog. What sapA homolog does the strain produce? What has been altered to achieve a strain that only sill produce a single S-layer protein? Have several sapA coding sequences been inactivated? If they have been inactivated, what are they? The stain of C.fetus is not clearly claimed.

Claim 11 defines the mutant strain to express a chimeric protein that includes a heterologous protein. What is the chimeric protein? Is it the combination of the SapA protein and the heterologous protein, or is it a chimeric protein that is distinct for one comprised of SapA and an additional coding sequence for an antigen? If the heterologous antigen is not in association with the native coding sequence of SapA, how is it expressed? Has a plasmid been introduced into the strain? Clarification of the relation of the various components of the mutant strain is requested.

Claim 12 is directed to a mixture of mutant C.fetus strains. The strains are defined to be a sapA chimera which is also a recA mutant. The claim recites the phrase "which is a recA mutant and refers back to both the sapA chimera and the C.fetus strain. Clarification of what the phrase "recA mutant" refers back to is requested.

Claim 12 recites two "wherein" clauses, the second of which seeks to clarify that "a single sapA homolog is mutated to encode a different chimeric protein representing a different heterologous antigen and each mutant is also RecA-deficient due to the mutation in recA. " Which strain of the mixture contains a single sapA homolog or do the strains contain multiple sapA homologs, but only a single sapA homolog is a chimera with a heterologous antigen coding sequence? Do all of the strains in the mixture contain different sapA homolog? How many different chimeric proteins are being expressed? How many different heterologous antigens are encoded by the mixture of the mutant strains? What does the phrase "sapA homolog is mutated to encode a different chimeric protein" mean? What is the encoded chimeric protein different from? No point of reference is defined to define a difference. In light of the fact that SapA proteins evidence recombination naturally and express heterologous antigens in nature, what is/are the heterologous antigens that the mixture of C.fetus strains encode?

The recA mutation, of claim 12, is not defined to be a mutation that eliminates expression of the RecA protein. The word deficient implies that there is some level of expression but it is deficient to some degree in comparison to the parent stain. What is the deficient level? What is the mutation in the recA open reading frame? While it is clear that there is a mutation in recA,

the open reading frame, the mutation need not eliminate expression. If the mutation is the deletion of the open reading frame for RecA then, the recitation of the phrase "a recA mutation" that implies the presence of the coding sequence, is not in agreement with the fact that no expression of RecA is obtained. Clarification of what mutation results in a RecA deficient strain is requested.

Claim 13 recites the word "immunogen" which lacks antecedent basis in claim 12 from which it depends. What is the immunogen? Is the immunogen the heterologous protein or the C.fetus strain? How many heterologous antigens are being administered? What are the pharmaceutically effective amounts of the heterologous antigens since the antigens are not specifically defined in the claims. What is the antigen effective for? Are the immunogen and the antigen intended to be the same or different components the composition? Clarification is requested.

Claim 15 has been amended to be an independent claim directed to a mutant strain of E.coli. As E.coli is known to produce homologs of a Type I secretion system, what is the source of the sapD, sapE and sapF genes? The source of the genes recited in the claim may be any source. The recitation of an abbreviation in the claim is permitted providing the term is defined at its first appearing. Clarification of the meaning of sapCDEF, relative to the source of the genes, and what the meaning of the term is.

Claim 16 defines the chimeric protein to comprise sequences of heterologous origin. The claim recites the singular form "heterologous protein" and then recites the plural "sequences of

heterologous origin." How many sequences are contained in the E.coli? What are they? What are the sequences that direct the secretion of the chimeric protein to the cell surface? What are the sequences that direct the binding of the chimeric protein to the lipopolysaccharide? What must nucleic acid sequences must the mutant cell have in association heterologous protein coding sequence in order for the functional limitations of the claim to be met? The claim only defines structural nucleic acid components based upon functional limitations. What the sequences are that afford the functional limitations is not distinctly claimed.

Claim 18 recites the phrase "wherein all but one of the seven to nine sapA homologs are altered" and depends from claim 1. Claim 1 does not provide antecedent basis for the recitation of seven to nine sapA homologs. How can a single DNA cassette alter all seven sapA homologs and leave one unaltered? Clarification of the claimed invention is requested.

Conclusion

33. This is a non- final action.

34.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp
September 25, 2001

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